Published in final edited form as:

AIDS Care. 2012 July ; 24(7): 820–827. doi:10.1080/09540121.2011.642989.

Hepatitis C Virus Infection is Associated with Painful Symptoms in HIV-infected Adults

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Abstract

The study aim was to assess whether HCV was associated with painful symptoms among patients with HIV. Using data from a prospective cohort of HIV-infected adults with alcohol problems we assessed the effects of HCV on pain that interfered with daily living and painful symptoms (muscle/joint pain, headache and peripheral neuropathy). Exploratory analyses assessed whether depressive symptoms and inflammatory cytokines mediated the relationship between HCV and pain. HCV-infected participants (n=200) had higher odds of pain that interfered with daily living over time (adjusted odds ratio [AOR] 1.43; 95% CI 1.02 to 2.01; p=0.04) compared to those not infected with HCV. HIV/HCV co-infected participants had higher odds of muscle or joint pain (AOR 1.45; 95% CI 1.06 to 1.97; p=0.02) and headache (AOR 1.57; 95% CI: 1.18 to 2.07; p<0.01). The association between HCV and peripheral neuropathy did not reach statistical significance (AOR 1.33; 0.96 to 1.85; p=0.09). Depressive symptoms and inflammatory cytokines did not appear to mediate the relationship between HCV and pain. Adults with HIV who are also co-infected with HCV are more likely to experience pain that interfered with daily living, muscle or joint pain, and headaches compared to those not co-infected. Research is needed to explore the association between HCV infection and pain, and to determine whether HCV treatment is an effective intervention.

Keywords

Pain; hepatitis C; cytokines; symptoms; peripheral neuropathy

Introduction

Pain is a common condition in HIV-infected patients. A nationally representative survey conducted in 1996 reported that 67% of HIV-infected persons in the United States had

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The authors report no institutional or commercial affiliations that might pose a conflict of interest.

Financial Disclosure: This study was supported by funding from the National Institute on Alcohol Abuse and Alcoholism (NIAAA) R01-AA13216 and K24-AA015674 and the National Institute on Drug Abuse (NIDA) K23-DA027367.

experienced pain in the previous 4 weeks.(Dobalian, Tsao, & Duncan, 2004) Pain is among the most common of symptoms reported by HIV-infected patients, and is strongly correlated with quality of life and psychological distress.(Breitbart, et al., 1998; Vogl, et al., 1999) Substance abuse and unhealthy alcohol use, which commonly occur in the context of HIV-infection,(Samet, Phillips, Horton, Traphagen, & Freedberg, 2004) may represent maladaptive coping responses to pain.(Brennan, Schutte, & Moos, 2005; Holahan, Moos, Holahan, Cronkite, & Randall, 2001) A better understanding of the etiology of pain in HIV-infected individuals is needed to effectively prevent and treat pain in this population.

A co-morbidity whose contribution to pain among HIV-infected persons has been relatively unexplored is infection with hepatitis C virus (HCV). Chronic HCV infection has been associated with painful diagnoses such as peripheral neuropathy, arthritis, and arthralgias, (Cacoub, et al., 2000) as well as generalized pain in quality of life studies.(Spiegel, et al., 2005) Individuals with HCV have been noted to have a high prevalence of chronic pain and treatment for pain.(Silberbogen, Janke, & Hebenstreit, 2007; Whitehead, et al., 2008) and a study of substance users found that those who were HCV-infected were more likely to have persistent pain compared to those who were uninfected.(Caldeiro, et al., 2008) The majority of injection drug users are infected with HCV,(Garfein, Vlahov, Galai, Doherty, & Nelson, 1996; Lorvick, Kral, Seal, Gee, & Edlin, 2001; Murrill, et al., 2002; Thomas, et al., 1995) and 15–30% of HIV-infected individuals are co-infected with HCV because of the shared risk factor of injecting drugs.(Sulkowski & Thomas, 2003) Injection drug use (IDU) has been associated with greater pain in some studies of HIV-infected individuals,(Del Borgo, et al., 2001; Dobalian, et al., 2004; Martin, Pehrsson, Osterberg, Sonnerborg, & Hansson, 1999; Riley, et al., 2003) and underlying HCV infection may be an unrecognized contributory factor.

A number of causal mechanisms can be hypothesized to explain an association between HCV and pain. Depression, which is a known risk factor for pain in patients with(Richardson, et al., 2009; Riley, et al., 2003; Tsao, Dobalian, & Naliboff, 2004) and without HIV(Bair, Robinson, Katon, & Kroenke, 2003), is a common co-morbidity among patients with HCV.(Dwight, et al., 2000; el-Serag, Kunik, Richardson, & Rabeneck, 2002; Fontana, et al., 2002; Golden, O'Dwyer, & Conroy, 2005; Lee, Jamal, Regenstein, & Perrillo, 1997) Among HIV-infected patients, co-infection with HCV has been shown to be independently associated with depressive symptoms.(Libman, et al., 2006) HCV may cause a cytokine-induced depression; a small study demonstrated correlations between plasma levels of interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α) and depressive symptoms.(Loftis, Huckans, Ruimy, Hinrichs, & Hauser, 2008) Researchers have also suggested that HCV may predispose to chronic pain conditions such as fibromyalgia through a cytokine-mediated pathway.(Thompson & Barkhuizen, 2003)

The primary aim of this study was to evaluate whether HCV status was associated with pain that interfered with daily living and painful symptoms in a cohort of HIV-infected adults with alcohol problems. A secondary aim was to explore whether depressive symptoms and serum levels of the inflammatory cytokines TNF- α , IL-6, and IL-10 mediated the relationship between HCV infection and pain.

Materials and Methods

Design

Data were obtained from a prospective, observational cohort study (HIV-Longitudinal Interrelationships of Viruses and Ethanol [HIV-LIVE]), in which assessments occurred at 6-month intervals over a maximum of 48 months.

Subjects

Recruitment occurred from a previous cohort study, an intake clinic for HIV-infected patients, HIV primary care and specialty clinics at two hospitals, homeless shelters, drug treatment programs, subject referrals, and flyers. Enrollment occurred between August 2001 and July 2003. Eligibility criteria were as follows: 1) documented HIV antibody test by ELISA and confirmed by Western blot; 2) two or more affirmative responses to the CAGE alcohol screening questionnaire, or physician investigator diagnosis of alcoholism; and 3) ability to speak English or Spanish. Exclusion criteria included: 1) scoring <21 on the 30-item Folstein Mini-Mental State Examination (i.e., cognitive impairment); and 2) inability to provide informed consent. The Institutional Review Boards of Boston Medical Center and Beth Israel Deaconess Medical Center approved this study. Informed consent was obtained from each patient and the protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki.

Outcomes

The primary outcome was any pain interference with daily life, which was measured using a single question from the SF-12 (Ware, Kosinski, & Keller, 1996): "During the past 4 weeks, how much did pain interfere with your normal work (including housework)?" Pain interference was defined as any response other than "not at all." Secondary outcomes were musculoskeletal pain, headache, and peripheral neuropathy. These symptoms were measured using the HIV Symptom Index (Justice, et al., 2001). This index is a validated 20-question inventory of symptoms common in the setting of HIV infection which assesses their frequency and consequences in the prior month. The questions asked: "How much have you been bothered by each of the following symptoms: 1) muscle aches or joint pain; 2) headache; and 3) pain, numbness or tingling in the hands and feet (peripheral neuropathy)?" Headache, muscle/joint pain, and peripheral neuropathy were defined as a response other than "I do not have this symptom." The primary and secondary outcomes were assessed at baseline and each follow-up visit.

Independent Variables

The main independent variable was chronic HCV infection, as defined as a positive HCV antibody result confirmed with detectable HCV RNA level on polymerase chain reaction (PCR) testing. Participants who were HCV antibody-positive and HCV RNA-negative were considered not to have chronic HCV infection (i.e. they had cleared their infection either spontaneously or through treatment). HCV status was assessed only at baseline. Covariates included in the analyses were age, sex, race (black v. non-black), current marital status (married v. not married), current smoking, past 6 months homelessness past 6 months any injection drug use, past month any heavy alcohol use, low CD4 count (<200 cells/ μ L), HIV viral load (detectable v. undetectable), HIV medication use in the past 6 months, depressive symptoms, and baseline serum levels of inflammatory cytokines TNF- α , IL-6, and IL-10. Hazardous alcohol use was defined as: 1) drinking greater than 14 standard drinks per week, or greater than 4 drinks in a day, for men; or 2) drinking greater than 7 drinks in the past week or greater than 3 drinks in a day for women. (Saitz, 2005) Depressive symptoms were measured using the Center for Epidemiologic Studies Depression Scale (CES-D), and a threshold of ≥ 23 was used to define substantial depressive symptoms. (Golub, et al., 2004) The cytokines TNF- α , IL-6, and IL-10 were chosen based on prior research demonstrating that 1) serum levels are significantly different in the setting of HCV infection compared to controls (Jacobson Brown & Neuman, 2001) and 2) they play a potential role in the pathogenesis of central pain conditions and chronic pain. (Jacobson Brown & Neuman, 2001; Uceyler & Sommer, 2008; Verri, et al., 2006; Watkins, Hutchinson, Milligan, & Maier, 2007) TNF- α and IL-6 were measured using Bio-Rad Luminex Flow Cytometry (Millipore) and IL-10 was measured using Chemiluminescent ELISA (R&D Systems). Laboratory

testing was conducted at the University of Vermont's Laboratory for Clinical Biochemistry Research.

Statistical Analyses

Chi-square and Student's t tests were used to compare baseline characteristics of subjects with and without chronic HCV infection. General estimating equations (GEE) logistic regression was used to calculate odds ratios and 95% confidence intervals for each pain outcome. The GEE approach was used to account for the correlation from using repeated observations from the same subject over time. An exchangeable working correlation structure was used, and empirical standard errors are reported for all analyses. Collinearity of covariates was assessed by calculating the correlation between independent variables, and no pair of variables had a Spearman correlation >0.40 . A two-tailed p value <0.05 was considered statistically significant for all hypothesis testing. Final models were adjusted for all covariates. Covariates except for age, sex, and race were all modeled as time-dependent. Based on the approach described by Baron and Kenny, (Baron & Kenny, 1986) exploratory analyses were performed to assess whether depressive symptoms and serum levels of cytokines TNF- α , IL-6, and IL-10 mediated the association between HCV infection and pain outcomes. As such, models that included and excluded depressive symptoms and inflammatory cytokines were compared to assess whether HCV coefficient estimates were attenuated by inclusion of the potential mediators. All subjects had data on depressive symptoms, however, only 309 had data on IL-6 and 343 had data on TNF- α and IL-10 due to insufficient serum sample for testing. Indicator variables were used to create a category for missing values for inflammatory cytokines so that the same subset of respondents was examined in each analysis. All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Inc., NC, USA).

Results

Of the 400 participants in the HIV-LIVE cohort, 397 had been tested for HCV RNA and were included in the analysis. Of the 397 HIV-infected subjects, 200 (50.4%) were found to have detectable HCV RNA and were considered to be co-infected. Participants who were HCV-infected were more likely to be older, homeless, have recently used injection drugs, diabetes, and have substantial depressive symptoms (Table 1). At baseline, the prevalence of having pain that interfered with daily living, muscle or joint pain, headache, and peripheral neuropathy was higher among HIV-infected participants who were co-infected with HCV compared to those who were not. HCV-infected participants were also significantly more likely to have baseline levels above the median for IL-6 and IL-10.

The median follow-up was 23.7 months (IQR: 12.2 to 31.7 months); the median number of follow-up assessments was 6 (IQR: 4 to 7). Analyses of longitudinal data included 2371 observations from 397 subjects. Results from final GEE logistic regression models (adjusted for time, age, sex, black race, marital status, homelessness, smoking, hazardous alcohol use, injection drug use, low CD4 count, detectable HIV viral load, use of HIV medications, and additional adjustment for diabetes for peripheral neuropathy outcome) are presented in row 1 of Table 2. Participants who were HCV-infected had significantly higher odds for experiencing pain that interfered with daily living over time (adjusted odds ratio [AOR] 1.43; 95% CI 1.02 to 2.01) compared to those who were not HCV-infected. Likewise, HCV-infected participants were more likely to experience muscle or joint pain (AOR 1.45; 95% CI 1.06 to 1.97) and headache (AOR 1.57; 95% CI: 1.18 to 2.07) over time compared to those who were not HCV-infected. The relative odds for HCV associated with peripheral neuropathy, while also greater than 1, did not reach statistical significance (AOR 1.33; 0.96 to 1.85).

The additional adjustment for substantial depressive symptoms somewhat attenuated the OR for HCV for all four pain outcomes (Table 2), suggesting that some of the association between HCV and pain may be explained by a greater burden of depressive symptoms in that group. However the degree of attenuation was low (<10% in all models) suggesting depression is not a mediator of the relationship between HCV and pain. In the multivariate models, depressive symptoms were strongly associated with pain interference (AOR 1.99; 1.60 to 2.48; $p<0.01$), muscle or joint pain (AOR 2.35; 1.88 to 2.93; $p<0.01$), headache (AOR 2.25; 1.86 to 2.71; $p<0.01$), and peripheral neuropathy (AOR 1.54; 1.27 to 1.87; $p<0.01$), and therefore, depressive symptoms may be a weak confounder. Levels of IL-6, IL-10 and TNF- α , however, were not significantly associated with any pain outcomes in multivariate models, and adjustment for these factors did not substantially impact the HCV effect in any model.

Discussion

In this cohort of HIV-infected persons with alcohol problems, co-infection with HCV was found to be associated with greater odds of experiencing pain that interfered with daily living, as well as symptoms of muscle or joint pain and headache. Although pain has been demonstrated to affect the majority of HIV-infected persons, (Dobalian, et al., 2004; Hewitt, et al., 1997; Vogl, et al., 1999) the mechanisms that underlie pain in this population are relatively poorly understood. Co-infection with HCV may be an overlooked and potentially modifiable risk factor for pain.

Substance use, and in particular IDU, has been associated with increased risk for pain at baseline and over time in HIV-infected patients. (Del Borgo, et al., 2001; Dobalian, et al., 2004; Martin, et al., 1999; Richardson, et al., 2009; Riley, et al., 2003; Tsao, Dobalian, & Stein, 2005) A study by Tsao et al demonstrated that HIV-related disease burden mediated the association between illicit drug use and pain in a longitudinal cohort of HIV-infected persons. (Tsao, et al., 2005) However, no published studies to date have examined the specific contributions of HCV co-infection to pain among persons living with HIV infection. Because HCV is strongly associated with IDU and has weaker associations with other drug use, (Armstrong, et al., 2006) it may be contributing to associations between substance use and pain observed in other studies. Our findings suggest that HCV may independently contribute to pain in HIV-infected patients. As prior studies have demonstrated the relative safety and efficacy of anti-HCV therapy among individuals with HIV, (Carrat, et al., 2004; Torriani, et al., 2004) the potential to modify or prevent painful symptoms may provide additional motivation for addressing HCV in co-infected patients.

Our results demonstrating an association between HCV infection and muscle and joint pain are consistent with background studies in non-HIV-infected populations. Quality of life studies using the SF-36 have demonstrated greater bodily pain among patients who are HCV-infected versus -uninfected. (Spiegel, et al., 2005) Clinical manifestations of HCV include extra-hepatic painful conditions. In a large series of HCV-infected subjects, the prevalence of arthralgias and neuropathy was found to be 19% and 9%, respectively. (Cacoub, et al., 2000) A study of chronic liver disease patients found that HCV-infected patients had a higher relative odds for musculoskeletal pain compared to uninfected patients. (Barkhuizen, et al., 1999) To our knowledge, however, no prior studies have reported an association between HCV and headache. There is evidence, however that HCV can be neuroinvasive, (Laskus, et al., 2005) and a large body of research demonstrates links between HCV and neurocognitive dysfunction. (Perry, Hilsabeck, & Hassanein, 2008) The fact that HCV was associated with pain at multiple sites could suggest that infection with HCV affects one's overall tolerance of pain. Studies of pain tolerance using experimental techniques such as cold-pressor test have found differences in pain thresholds between

opioid dependent former injection drug users and controls.(Compton, Charuvastra, Kintaudi, & Ling, 2000; Compton, Charuvastra, & Ling, 2001; Doverty, et al., 2001) It is conceivable that HCV status could, in part, be responsible for these differences.

We explored whether depressive symptoms and increased levels of inflammatory cytokines were mediators of the relationship between HCV and pain. Adjustment for depressive symptoms did not substantially attenuate the effects of HCV suggesting it is not a mediator. Results of the exploratory analyses also did not support that higher baseline levels of inflammatory cytokines were part of the causal pathway between HCV and pain. However, caution must be taken with interpreting these results as there were a number of limitations to the analyses. We measured serum levels of inflammatory cytokines at baseline only, and it is possible that changes in cytokine levels over time might better correlate with pain. Second, serum cytokine levels might not reflect the relevant physiologic pathway as cytokine expression can occur in other compartments (cerebrospinal fluid, peripheral blood mononucleocytes).(Loftis, Huckans, & Morasco)

There are additional limitations to this study. The main study outcome was based on a single question on the SF-12 questionnaire that reflected pain over the past 4 weeks. There was no information on pain severity, duration, or treatment available for analysis. Our findings could be related to undertreatment of pain among HCV-infected persons. Prior research has suggested that HIV-infected injection drug users are less likely to have pain effectively treated than those who do not use injection drugs.(Breitbart, et al., 1997) It is also possible that providers who care for patients with HCV infection may be reluctant to prescribe certain pain medications because of concerns about potential hepatotoxicity. The study was conducted on a population of HIV-infected adults with alcohol problem, which may affect the generalizability of its findings. However, given the prevalence of past alcohol problems among HIV-infected individuals, up to 40% in some studies,(Samet, et al., 2004) these findings would still be of importance even if not more broadly applicable. There may be other unmeasured confounders such as stress or anxiety associated with HCV infection that were not addressed in the analysis.

In summary, this study of HIV-infected adults with alcohol problems found that participants who were co-infected with HCV were more likely to experience pain that interfered with daily living, muscle or joint pain, and headaches over time compared to those who were HCV-negative. Given that pain is a common morbidity among HIV-infected patients, more research is needed to explore the association between chronic HCV infection and pain in this population, and whether HCV treatment improves pain.

Acknowledgments

The authors thank Na Wang for her data management support.

List of Abbreviations

HIV	Human immunodeficiency virus
HCV	Hepatitis C virus
IDU	Injection drug use
TNF-α	Tumor necrosis factor α GEE, General estimating equations
HIV-LIVE	HIV-Longitudinal Interrelationships of Viruses and Ethanol
GEE	General estimating equations

IQR	Interquartile range
AOR	Adjusted odds ratio

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Table 1

Baseline Characteristics of HIV-Infected Participants with and without HCV

	HCV negative (n=197)	HCV positive (n=200)	
	Number (%)	Number (%)	p-value
Age (Mean/SD)	41 ($\pm$ 8)	44 ($\pm$ 7)	<0.01
Female	46 (23%)	54 (27%)	0.4
Black	87 (44%)	76 (38%)	0.21
Married	14 (7%)	13 (7%)	0.81
Smoker	145 (74%)	158 (79%)	0.21
Homeless *	40 (20%)	58 (29%)	0.04
Injection Drug Use *	9 (5%)	47 (24%)	<0.01
Heavy Alcohol Use **	66 (34%)	58 (29%)	0.32
Low CD4 Count (<200 cells/ μ L)	33 (17%)	41 (21%)	0.4
Depressive Symptoms ($\geq$ 23 on CES-D)	72 (37%)	120 (60%)	<0.01
Diabetes	8 (4%)	20 (10%)	0.02
Pain That Interferes with Daily Living	122 (62%)	144 (72%)	0.03
Muscle or Joint Pain	129 (66%)	153 (77%)	0.02
Headache	97 (49%)	132 (66%)	<0.01
Peripheral Neuropathy	110 (56%)	136 (68%)	0.01
TNF- α (Median/IQR)	6.5 (4.4 to 8.9)	7.6 (5.1 to 10.8)	
TNF- α above Median	81 (46%)	90 (54%)	0.15
IL-6 (Median/IQR)	2.1 (1.3 to 3.5)	3.4 (2.0 to 5.7)	
IL-6 above Median	64 (40%)	90 (61%)	<0.01
IL-10 (Median/IQR)	4.2 (2.5 to 6.6)	6.2 (4.0 to 9.3)	
IL-10 above Median	68 (39%)	103 (62%)	<0.01

* Use in the past 6 months.

** Use in the past month.

Table 2

Odds Ratios for the Association between HCV and Pain Outcomes

	Pain that Interferes with Living			Muscle or Joint Pain			Headache			Peripheral Neuropathy		
	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value	OR	95% CI	p-value
Final Model*	1.43	1.02 – 2.01	0.04	1.45	1.06 – 1.97	0.02	1.57	1.18 – 2.07	<0.01	1.33	0.96 – 1.85	0.09
Final Model + Depressive Symptoms	1.34	0.96 – 1.88	0.09	1.33	0.98 – 1.81	0.07	1.44	1.09 – 1.90	0.01	1.27	0.92 – 1.77	0.15
Final Model + Depressive Symptoms + high IL-6 (above median)	1.34	0.95 – 1.89	0.10	1.34	0.98 – 1.83	0.06	1.43	1.08 – 1.91	0.01	1.31	0.94 – 1.83	0.11
Final Model + Depressive Symptoms + high IL-10 (above median)	1.29	0.91 – 1.83	0.15	1.27	0.94 – 1.74	0.12	1.42	1.07 – 1.88	0.01	1.29	0.93 – 1.79	0.12
Final Model + Depressive Symptoms + high TNF- α (above median)	1.30	0.92 – 1.83	0.13	1.33	0.98 – 1.81	0.07	1.46	1.11 – 1.93	<0.01	1.29	0.93 – 1.79	0.12

* GEE logistic regression models adjusted for time, age, sex, black race, marital status, homelessness, smoking, hazardous alcohol use, injection drug use, low CD4 count (<200), HIV viral load and use of HIV medications; additional adjustment for diabetes for peripheral neuropathy outcome.